Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/821,583	**Applicant(s)** WANG ET AL.	
	Examiner Richard G. Hutson	**Art Unit** 1652	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 19 February 2009 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires *6* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *19 February 2009*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1-26*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/Richard G Hutson/
Primary Examiner, Art Unit 1652

Continuation of 11. does NOT place the application in condition for allowance because:
Claims 1-26 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.
Applicants continue to submit that the standard for written description is that one of skill must demonstrate possession of the claimed invention and f a genus, this can be achieved by description of representative species or providing general structural characteristics in combination with function. Applicants submit that the specification provides such description in that applicants have disclosed any number of polymerases that can be modified using a nucleic acid binding domain as claimed, for example, Taq polymerase.
Applicants continue to submit that the specification not only fully describes polymerases for use in the invention, but also provides description of Sso7d nucleic acid binding domains as recited in the claims, such as the structural feature of the genus of Sso7d proteins for use in the invention, i.e., reference SEQ ID NO:2, and provides structural and functional characteristics of proteins encompassed by the genus. Applicants further submit that the specification further describes references that disclose other Sso7d homologs and describes structural analyses of Sso7d and Sac7d when bound to DNA. Applicants continue to submit that the application also teaches that this DNA binding function can be used as a basis for selecting DNA binding domains that can be used to enhance polymerase processivity.
Applicant's complete argument continues to be acknowledged and has been carefully considered, however, are found nonpersuasive for the reasons previously made of record and repeated herein.
It continues that while applicants have disclosed any number of polymerases that can be modified using a nucleic acid binding domain as claimed, it is pointed out to applicants that while applicants do list a number of polymerases as a number of polymerases are known, applicants only teach that two, Delta Taq and Pfu DNA polymerase, of the many known polymerases are able to have their processivity enhanced as a result of the joining of a double stranded nucleic acid binding domain.
Beyond the few disclosed species, it continues that applicants do not describe any other species of the claimed genus or describe this double stranded nucleic acid binding domain joined to any other polymerase domains. While homologs of the Sso7d protein may be known, it is not shown or clear that these homologs would have the same interaction with all polymerase domains.
Given this lack of additional representative species as encompassed by the claims, applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.
Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 1-26 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for those methods of amplifying a target nucleic acid, comprising the use of a protein comprising two heterologous domains, wherein the first domain is a sequence-non-specific-double-stranded nucleic acid-binding domain joined to a second domain which is a Taq or Pfu DNA polymerase domain, wherein said sequence-non-specific-double-stranded nucleic acid-binding domain is Sso7d comprising the amino acid sequence of SEQ ID NO: 2, does not reasonably provide enablement for any method of amplifying a target nucleic acid, comprising the use of a protein comprising two heterologous domains wherein the first domain is a sequence-non-specific-double-stranded nucleic-acid-binding domain joined to a second domain which is any polymerase domain, wherein the first domain is any sequence-non-specific-double-stranded nucleic acid-binding domain wherein said domain specifically binds to any polyclonal antibody generated against Sso7d, joined to any polymerase domain. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.
As above, applicants submit that the specification provides multiple examples of enhancement of processivity of polymerases using Sso7d and its homologs. Applicants submit that in addition to the general guidance regarding polymerases and Sso7d proteins provided by the specification, the examples provide data for four exemplary embodiments using two Sso7 proteins (Sso7d and Sac7d) and three polymerases (Taq, Delta-Taq, and Pfu). Applicants submit that these data provide further evidence that the claims are enabled.
Applicants have also provided a Declaration under 37 C.F.R. § 1.132 by Peter
Vander Horn ("the Vander Horn Declaration") in the parent application and Applicants respectfully request that the Declaration, a copy of which is enclosed, be made of record in the instant application, as the same issues are being raised. Applicants submit that the Vander Horn Declaration provides objective reasons further justifying the claimed genus of methods.
Applicants submit that the Sso7d nucleic acid binding domains set forth in the claims are not derived from a novel gene and a natural variation of about 76% occurs within the family (as noted in the Vander Horn Declaration, which is discussed in greater detail below).
Applicants submit that Analyses of the structures of Sso7d and Sac7d bound to DNA have been performed by several investigators and the specification directs a practitioner to exemplary references describing such studies .
Applicants submit that Similar x-ray crystallographic analysis has also been performed for the related protein Sac7d (e.g., Robinson, et al., Nature 392:202-205, 1998, which reference is cited by Gao et al.) and Gao et al. additionally compare the Sso7d-DNA complex to the Sac7d-DNA complex. Thus, the specification therefore properly enables the claimed methods. Applicants submit that they have provided objective reasons justifying the percent identity set forth in the claims. Applicants submit that not only does the subject specification provide a full disclosure of the family of Sso7 proteins, Applicants have provided the Vander Horn declaration, which provides objective reasons justifying the 75% level of identity recited in the claims. Applicants submit that Dr. Vander Horn explains that by following the differences between the family members, those of skill would immediately recognize where the critical and noncritical regions of the proteins are located and Applicants submit that as Dr. Vander Horn notes in his Declaration, to limit the claims to a percentage above that found within the naturally occurring variants is to ignore that nature has provided this road map for introducing mutations.
Applicants further submit that in addition to the natural variations between family members, any competent protein chemist readily understands that non-naturally occurring but conserved substitutions are possible throughout the primary sequences of the prototype proteins as Dr. Vander Horn explains this conventional wisdom at section 9 of his Declaration.
Applicants submit that furthermore, Dr. Vander Horn explains at section 10 of his Declaration that the structural features of the

Archaeal protein interaction with DNA had been previously studied by workers such as Gao et al. Dr Vander Horn details how this information permits a practitioner to identify the critical binding domains in the proteins, which allows one of skill to focus mutations away from these critical regions so that amino acid residues may be substituted without compromising activity.
Applicants submit that the Vander Horn Declaration thus further illustrates how one of skill in the art can use the large body of knowledge in the art to identify functional Sso7d variants having the percent identity set forth in the claims without undue experimentation.
In view of the foregoing, the application provides proper guidance such that one
of skill can identify a nucleic acid binding domain as claimed and that use it to modify
polymerase processivity with a reasonable expectation of success.
Applicant's complete argument continues to be acknowledged and has been carefully considered, however, is found nonpersuasive for the reasons previously made of record and repeated herein.
As above, with respect to applicants submission that the specification provides multiple examples of enhancement of processivity of polymerases using Sso7d and its homologs, the provided examples, using two Sso7 proteins (Sso7d and Sac7d) and three polymerases (Taq, Delta-Taq, and Pfu) are insufficient to enable the breadth of the claimed genus of methods of amplifying a target nucleic acid comprising the use of any sequence-non-specific double-stranded nucleic-acid-binding domain that comprises an amino acid sequence that has a mere 75% identity to the amino acid sequence of SEQ ID NO:2 and is joined to any polymerase domain with error-correcting activity, where the sequence non-specific double-stranded nucleic-acid-binding domain enhances the processivity of the polymerase domain compared to an identical polymerase domain not having the sequence non-specific double-
stranded nucleic acid binding domain.
It is appreciated that with regard to naturally occurring 7kDa proteins in the family of Archael DNA-binding proteins there are many family members reported in the literature and these are evolutionarily related allowing for mutations in these domains to be made while conserving the double stranded DNA binding ability.
It continues to be recognized that the art provides knowledge as to a great number of polymerases and additionally knowledge regarding the DNA binding domain of Sso7d and related homologs, however, it is the lack of teaching and knowledge of the interaction between the various polymerases as encompassed by the claimed methods and the ability of Sso7d homologs to increase the processivity of a polymerase domain that is key to applicants claimed invention. It is the knowledge and guidance related to this relationship and interaction between the two different domains that is absent in the art and applicants specification. For this reasons applicants have not sufficiently enabled the breadth of the claimed genus of methods comprising the use of a protein comprising two heterologous domains wherein the first domain is a sequence-non-specific-double-stranded nucleic-acid-binding domain joined to a second domain which is any polymerase domain, wherein the first domain is any sequence-non-specific-double-stranded nucleic acid-binding domain wherein said domain specifically binds to any polyclonal antibody generated against Sso7d, joined to any polymerase domain
As stated previously and above, with regard to applicants submission that the Sso7d nucleic acid binding domains set forth in the claims are not derived from a novel gene and a natural variation of about 76% occurs within the family (as discussed in the Vander Horn Declaration) this variation within the family of proteins does not offer sufficient guidance as to those necessary features that result in the claimed increase in processivity of a joined DNA polymerase domain. It is likely that this complex interaction is a result of factors of both the double stranded nucleic acid binding domain as well as the specific polymerase domain itself. Applicants have not addressed this interaction.
In view of the foregoing, the application provides insufficient guidance such that one of skill could not identify those nucleic acid binding domains encompassed in the claims and use it to modify any polymerase domain's processivity with a reasonable expectation of success. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of those proteins and methods of their use having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claims 1-26 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 11, 15, 16 and 22 of copending Application No. 10/306,827. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 11, 15, 16 and 22 of 10/306,827 drawn to a method of increasing the yield of from a polymerase reaction on a target sequence comprising contacting the target nucleic acid with a polymerase joined to a sequence non-specific-nucleic - acid-binding domain anticipate claims 1-14 drawn to a method of amplifying a target nucleic acid, comprising the use of a protein comprising two heterologous domains wherein the first domain is a sequence-non-specific-double-stranded nucleic-acid-binding domain joined to a second domain which is a DNA polymerase domain, wherein the first domain is any sequence-non-specific-double-stranded nucleic-acid-binding domain wherein said domain specifically binds to any polyclonal antibody generated against Sso7d, joined to any DNA polymerase domain. While the preambles of the different claims are different, the method steps of the claims of 10/306,827 anticipate the instant claims.
This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.
Applicant's acknowledgement of this provisional rejection and statement that they will consider the filing of a terminal disclaimer to obviate the rejection is acknowledged..